Epidermal growth factor receptor targeted therapy in stages III and IV head and neck cancer

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ABSTRACT

Question

What are the benefits associated with the use of anti–epidermal growth factor receptor (anti-EGFR) therapies in squamous cell carcinoma of the head and neck (HNSCC)? Anti-EGFR therapies of interest included cetuximab, gefitinib, lapatinib, zalutumumab, erlotinib, and panitumumab.

Perspectives

Head-and-neck cancer includes malignant tumours arising from a variety of sites in the upper aerodigestive tract. The most common histologic type is squamous cell carcinoma, and most common sites are the oral cavity, the oropharynx, the hypopharynx, and the larynx. Worldwide, HNSCC is the sixth most common neoplasm, and despite advances in therapy, long-term survival in HNSCC patients is poor. Primary surgery followed by chemoradiation, or primary chemoradiation, are the standard treatment options for patients with locally advanced (stages III–IVB) HNSCC; however, meta-analytic data indicate that the benefit of concurrent platinum-based chemotherapy disappears in patients over the age of 70 years.

Cetuximab is a monoclonal antibody approved for use in combination with radiation in the treatment of patients with untreated locally advanced HNSCC and as monotherapy for patients with recurrent or metastatic (stage IVC) HNSCC who have progressed on platinum-based therapy.

Given the interest in anti-EGFR agents in advanced HNSCC, the Head and Neck Cancer Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC) chose to systematically review the literature pertaining to this topic so as to develop evidence-based recommendations for treatment.

Outcomes

Outcomes of interest included overall and progression-free survival, quality of life, tumour response rate and duration, and the toxicity associated with the use of anti-EGFR therapies.

Methodology

The MEDLINE, EMBASE, and Cochrane Library databases, the American Society of Clinical Oncology online conference proceedings, the Canadian Medical Association InfoBase, and the National Guidelines Clearinghouse were systematically searched to locate primary articles and practice guidelines. The reference lists from relevant review articles were searched for additional trials. All evidence was reviewed, and that evidence informed the development of the clinical practice guideline. The resulting recommendations were approved by the Report Approval Panel of the PEBC, and by the Head and Neck Cancer DSG. An external review by Ontario practitioners completed the final phase of the review process. Feedback from all parties was incorporated to create the final practice guideline.

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Results

The electronic search identified seventy-four references that were reviewed for inclusion. Only four phase III trials met the inclusion criteria for the present guideline. No practice guidelines, systematic reviews, or meta-analyses were found during the course of the literature search.

The randomized controlled trials (RCTs) involved three distinct patient populations: those with locally advanced HNSCC being treated for cure, those with incurable advanced recurrent or metastatic HNSCC being treated with first-line platinum-based chemotherapy, and those with incurable advanced recurrent or metastatic HNSCC who had disease progression despite, or who were unsuitable for, first-line platinum-based chemotherapy.

Practice Guideline

These recommendations apply to adult patients with locally advanced (nonmetastatic stages III–IVB) or recurrent or metastatic (stage IVC) HNSCC.

- Platinum-based chemoradiation remains the current standard of care for treatment of locally advanced HNSCC.
- In patients with locally advanced HNSCC who are medically unsuitable for concurrent platinum-based chemotherapy or who are over the age of 70 years (because concurrent chemotherapy does not appear to improve overall survival in this patient population), the addition of cetuximab to radical radiotherapy should be considered to improve overall survival, progression-free survival, and time to local recurrence.
- Cetuximab in combination with platinum-based combination chemotherapy is superior to chemotherapy alone in patients with recurrent or metastatic HNSCC, and is recommended to improve overall survival, progression-free survival, and response rate.
- The role of anti-EGFR therapies in the treatment of locally advanced HNSCC is currently under study in large randomized trials, and patients with HNSCC should continue to be offered clinical trials of novel agents aimed at improving outcomes.

Qualifying Statements

Chemoradiation is the current standard of care for patients with locally advanced HNSCC, and to date, there is no evidence that compares cetuximab plus radiotherapy with chemoradiation, or that examines whether the addition of cetuximab to chemoradiation is of benefit in these patients. However, five ongoing trials are investigating the effect of the addition of EGFR inhibitors concurrently with, before, or after chemoradiotherapy; those trials should provide direction about the best integration of cetuximab into standard treatment.

In patients with recurrent or metastatic HNSCC who experience progressive disease despite, or who are unsuitable for, first-line platinum-based chemotherapy, gefitinib at doses of 250 mg or 500 mg daily, compared with weekly methotrexate, did not increase median overall survival [hazard ratio (HR): 1.22; 96% confidence interval (CI): 0.95 to 1.57; $p = 0.12$ (for 250 mg daily vs. weekly methotrexate); HR: 1.12; 95% CI: 0.87 to 1.43; $p = 0.39$ (for 500 mg daily vs. weekly methotrexate)] or objective response rate (2.7% for 250 mg and 7.6% for 500 mg daily vs. 3.9% for weekly methotrexate, $p > 0.05$). As compared with methotrexate, gefitinib was associated with an increased incidence of tumour hemorrhage (8.9% for 250 mg and 11.4% for 500 mg daily vs. 1.9% for weekly methotrexate).

KEY WORDS

Head-and-neck cancer, epidermal growth factor receptor, EGFR inhibitors, overall survival, progression-free survival, tumour response rate

1. QUESTION

What are the benefits associated with the use of anti-epidermal growth factor receptor (anti-EGFR) therapies in locally advanced, recurrent, or metastatic squamous cell carcinoma of the head and neck (HNSCC)?

Outcomes of interest included overall and progression-free survival, quality of life (QOL), tumour response rate and duration, and toxicities associated with the use of anti-EGFR therapies. Anti-EGFR therapies of interest included cetuximab, gefitinib, lapatinib, zalutumumab, erlotinib, and panitumumab.

2. CHOICE OF TOPIC AND RATIONALE

Head-and-neck cancer includes malignant tumours arising from a variety of sites in the upper aerodigestive tract. The most common histologic type is squamous cell carcinoma, and the most commonly affected sites are the oral cavity, the oropharynx, the hypopharynx, and the larynx [1]. Worldwide, HNSCC is the sixth most common neoplasm [2].

Despite advances in therapy, long-term survival in HNSCC patients remains poor. The 5-year relative survival rate, worldwide, from oral cancer is generally less than 50%. The poor 5-year survival rates have remained unchanged for more than three decades [1,2]. Primary surgery followed by chemoradiotherapy, or primary concurrent platinum-based chemoradiotherapy, are the standard treatment options for patients with locally advanced HNSCC [3]. However, meta-analytic data indicate that the benefit of concurrent chemotherapy disappears for patients over the age of 70 years [4]. Despite treatment advances, locoregional disease recurrence is still a major problem in patients with advanced disease. Local recurrences present

in about 10%–30% of cases involving advanced tumours, even with histopathologically tumour-free surgical margins after resection [5]. Historically, the standard treatment for recurrent or metastatic HNSCC has been platinum-based chemotherapy, although the benefits on survival and QOL are debatable [6].

A member of the ErbB family of receptor tyrosine kinases, EGFR is abnormally activated in epithelial cancers, including HNSCC [7,8]. More than 90% of HNSCC overexpresses EGFR, and higher levels of EGFR expression are associated with worse clinical outcomes [9]. Radiation increases the expression of EGFR in cancer cells, and blockade of EGFR signalling sensitizes cells to the effects of radiation [10]. Inhibition of EGFR signalling can be accomplished by small molecules, by monoclonal antibodies directed against ligands or receptors, and by immunotoxin conjugates [11].

Cetuximab (Erbitux, C225, IMC-225: ImClone Systems, Branchburg, NJ, U.S.A.) is a monoclonal antibody that binds competitively to EGFR and blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth, induction of apoptosis, and decreased production of matrix metalloproteinase and vascular endothelial growth factor [7,12,13]. Cetuximab was approved by Health Canada for the treatment of metastatic colorectal cancer in September 2005 [14]. It was also granted approval by the U.S. Food and Drug Administration (FDA) in March 2006 for use in combination with radiation in the treatment of patients with previously untreated locally advanced (stages III–IVB) HNSCC and for use as monotherapy in patients with recurrent or metastatic (stage IVC) HNSCC who have progressed on platinum-based therapy [15,16].

Given the interest in cetuximab and other anti-EGFR agents in advanced HNSCC, the Head and Neck Cancer Disease Site Group (DSG) of Cancer Care Ontario's Program in Evidence-Based Care (PEBC) chose to systematically review the literature pertaining to this topic so as to develop evidence-based recommendations for treatment.

3. METHODS

3.1 Guideline Development

The evidence-based series was developed by the PEBC using the methods of the practice guidelines development cycle [17,18]. For the present project, systematic review was the core methodology used to develop the evidentiary base. Evidence was selected and reviewed by two members of the Head and Neck Cancer DSG and two methodologists. The systematic review is a convenient and up-to-date source of the best available evidence on anti-EGFR targeted therapy.

The body of evidence in the present review comprises data primarily from mature randomized controlled trials (RCTs). That evidence forms the basis of a clinical practice guideline developed by the Head and Neck Cancer DSG. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent of its funding source.

3.2 Literature Search Strategy

The MEDLINE (1996 through February 2009, week 1), EMBASE (1996 to 2009, week 6), and Cochrane Library (2008, issue 4) databases were systematically searched for relevant articles. Search terms related to head-and-neck cancer, known EGFR inhibitors, and selected publication types and study designs: practice guidelines, systematic reviews, meta-analyses, reviews, RCTs, and controlled clinical trials. The American Society of Clinical Oncology (1996 to 2008) online conference proceedings were searched for reports of new or ongoing trials. The Canadian Medical Association InfoBase (mdm.ca/cpgsnew/cpgs/index.asp) and the National Guidelines Clearinghouse (www.guideline.gov/search/detailedsearch.aspx) were also searched for existing evidence-based practice guidelines. The reference lists from relevant review articles were searched for additional trials.

3.3 Study Selection Criteria

Articles were selected for inclusion in this systematic review if

- they were abstracts or full reports of randomized phase II or III trials of EGFR-targeted monoclonal antibodies, either alone or in combination with radiotherapy or chemotherapy, versus a control therapy (including radiotherapy, chemotherapy, chemoradiotherapy, or best supportive care) in the treatment of advanced HNSCC; and
- they reported at least one of the following outcomes: compliance, survival, time to progression, response duration, or response rate;

or if

- they were published reports of systematic reviews or evidence-based guidelines that addressed the guideline question.

Articles published in languages other then English were excluded because of limited translation resources.

3.4 External Review and Approval

The draft report underwent a two-pronged review process:

- A targeted peer review intended to obtain direct feedback on the draft report from a small number of specified content experts

- A professional consultation intended to facilitate dissemination of the final guidance report to Ontario practitioners

Four targeted physicians were sent a survey consisting of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and the overall quality and use of the practice guideline in clinical decision-making. Written comments were invited.

Individuals who chose to take part in the informal professional consultation were asked to rate the overall quality and use of the practice guideline in clinical decision-making.

The Head and Neck Cancer DSG reviewed the results of these two surveys.

4. RESULTS

4.1 Literature Search Results

The electronic search identified seventy-four references that were reviewed for inclusion. Only three trials in four reports met the inclusion criteria for the present guideline. In addition, one randomized phase III trial, published in abstract form at the American Association for Cancer Research 2007 annual meeting, was identified and met the inclusion criteria [19]. Table I describes the treatment arms, patient characteristics, and important quality elements of the included trials.

One RCT [10] studied radiation therapy (RT) with and without cetuximab in patients with locally advanced HNSCC treated curatively. Two randomized trials [6,20] examined the role of a platinum-based chemotherapy with and without cetuximab in patients with incurable advanced or metastatic HNSCC. A separate publication [21] reported QOL results from the foregoing RCT. One RCT [19] compared two different doses of daily gefitinib with weekly methotrexate in patients having incurable advanced recurrent or metastatic HNSCC who experienced disease progression despite, or who were unsuitable for, first-line platinum-based chemotherapy.

No practice guidelines, systematic reviews, or meta-analyses were found during the course of the literature search.

The RCTs involved three distinct patient populations: those with locally advanced (stages III–IVB) HNSCC being treated for cure, those with incurable advanced recurrent or metastatic (stage IVC) HNSCC being treated with first-line platinum-based chemotherapy, and those with incurable advanced recurrent or metastatic HNSCC who had failed or were unsuitable for first-line platinum-based chemotherapy. Performance was measured as either Karnofsky performance status or Eastern Cooperative Oncology Group score. Median age of the patients in the various studies ranged from 56 years to 60 years, with an overall range of 33–83 years. Primary tumour sites reported were the pharynx (5%–63%) and the larynx (23%–35%).

4.2 Outcomes

Table II reports data on overall survival, progression-free survival, and objective response rates from the included studies. Data about overall survival were not pooled because of a lack of information.

Bonner *et al.* [10] reported improvement with the addition of cetuximab to RT in patients with locally advanced HNSCC in terms of overall survival [hazard ratio (HR): 0.74; 95% confidence interval (CI): 0.57 to 0.97; $p = 0.03$], progression-free survival (HR: 0.70; 95% CI: 0.54 to 0.90; $p = 0.006$), locoregional control (24.4 months vs. 14.9 months; HR: 0.68; 95% CI: 0.52 to 0.89; $p = 0.005$), and objective response rate (74% vs. 64%, $p = 0.02$) [10]. Overall survival and progression-free survival rates at 3 years were 55% and 42% in the RT-plus-cetuximab group compared with 45% and 31% in the RT-alone group. Locoregional control remained greater in the RT-plus-cetuximab group at 1, 2, and 3 years (at 3 years: 47% vs. 34% for RT alone; $p < 0.01$).

Burtness *et al.* [6] reported a higher objective response rate in patients with recurrent or metastatic HNSCC receiving cetuximab plus cisplatin (26% vs. 10%, $p = 0.03$). Additionally, these authors reported that 9 of the 13 patients (69%) in the treatment crossover group had stable disease at 4 weeks. However, no statistically significant improvements in overall or progression-free survival were reported. It is doubtful this trial was truly adequately powered to assess its primary endpoint of progression-free survival; certainly it was underpowered to assess overall survival. In the subset of patients who crossed over to the cetuximab group upon disease progression, overall survival was reported as 3.9 months. At 1 and 2 years, overall survival was 38.6% and 15.8% with chemotherapy plus cetuximab compared with 31.7% and 9.4% with chemotherapy plus placebo.

Vermorken *et al.* [20] reported improved overall survival for patients with recurrent or metastatic HNSCC who received chemotherapy (cisplatin or carboplatin plus 5-fluorouracil) plus cetuximab compared with patients who received chemotherapy (cisplatin or carboplatin plus 5-fluorouracil) alone (median: 10.1 months vs. 7.4 months, $p = 0.04$). Additionally, these authors reported that progression-free survival (5.6 months vs. 3.3 months, $p < 0.001$) and the overall response rate (36% vs. 20%, $p < 0.001$) were greater in the cetuximab group than in the group receiving chemotherapy alone.

4.3 Toxicity

Bonner *et al.* [10] reported that grades 3–5 adverse effects were similar in both arms, except for acneiform rash ($p < 0.001$) and infusion-related reaction

TABLE I Patient characteristics and treatment regimens from phase III randomized controlled trials of epidermal growth factor receptor targeted therapy

Reference	*Patients (n)*	*Characteristics*	*Primary site (%)*	*Treatment regimen*
Radiation therapy (RT) plus cetuximab (C) in locally advanced HNSCC				
Bonner *et al.*, 2006 [10]	Arm A: 211	Non-metastatic Mean age: 56 years (RT+C), 58 years (RT)	Oropharynx: 56 Larynx: 27 Hypopharynx: 17	A: RT+C [initial dose 400 mg/m^2 intravenously (IV), then 250 mg/m^2 IV weekly for 6.0–7.0 weeks]
				vs.
	Arm B: 213	Age range: 34–83 years	Oropharynx: 63 Larynx: 24 Hypopharynx: 13	B: RT alone (once-daily RT: 2.0 Gy/fx, 5 fx/week for 7 weeks; or twice-daily RT: 1.2 Gy/fx, 10 fx/week for 6.0–6.5 weeks; or concomitant boost RT: 32.4 Gy once daily, 1.8 Gy/fx, 5 fx/week for 3.6 weeks; or 21.6 Gy/fx morning dose, 5 fx/week for 2.4 weeks, 18.0 Gy afternoon dose, 1.5 Gy/fx, 5 fx/week for 2.4 weeks)
	Total: 424			
Chemotherapy (CT) plus cetuximab (C) in recurrent or metastatic HNSCC				
Burtness *et al.*, 2005 [6]	Arm A: 57	Recurrent or metastatic (or both) Mean age: 60.6 years (CT+C), 58.3 years (CT)	Oropharynx: 31.6 Larynx: 22.8 Hypopharynx: 7.0	A: CT+C [CT: cisplatin 100 mg/m^2 IV day 1 every 4 weeks, plus C: 200 mg/m^2 IV day 1 over 120 min (cycle 1), then 125 mg/m^2 IV over 60 min (subsequent cycles) weekly]
	Arm B: 60		Oropharynx: 31.7 Larynx: 35.0 Hypopharynx: 5.0	B: CT+placebo [CT: cisplatin 100 mg/m^2 IV day 1 every 4 weeks, plus placebo: 200 mg/m^2 IV day 1 over 120 min (cycle 1), then 125 mg/m^2 IV over 60 min (subsequent cycles) weekly]
	Randomized: 117	ECOG performance status: 0 (42.1% CT+C, 40% CT); 1 (57.9% CT+C, 60% CT)		
Vermorken *et al.*, 2008 [20]	Arm A: 222	Recurrent or metastatic (or both) Median age: 57 years	Pharynx: 47 Larynx: 25	A: CT+C [CT: cisplatin (100 mg/m^2 IV day 1) or carboplatin (AUC 5 mg/mL/min IV, day 1) for a maximum of six 3-week cycles, plus 5-fluorouracil (1000 mg/m^2 daily continuous-infusion IV, first 4 days per cycle); plus C: initial dose 400 mg/m^2 IV day 1, then 250 mg/m^2 IV weekly, until progression or unacceptable toxicity]
	Arm B: 220	Age range: 33–80 years Mean Karnofsky performance status: 80 (range: 50–100)		B: CT [CT: cisplatin (100 mg/m^2 IV day 1) or carboplatin (AUC 5 mg/mL/min IV, day 1) for a maximum of six 3-week cycles, plus 5-fluorouracil (1000 mg/m^2 daily continuous-infusion IV, first 4 days per cycle)]
	Total: 442			
Gefitinib versus methotrexate in recurrent or metastatic HNSCC				
Stewart *et al.*, 2007 [19] (abstract)	Total: 486	Recurrent or metastatic (or both)	Not reported	A: Oral gefitinib 250 mg once daily B: Oral gefitinib 500 mg once daily C: Methotrexate 40 mg/m^2 IV weekly, with option to increase to 60mg/m^2 in the absence of unacceptable toxicity

HNSCC = head and neck squamous cell carcinoma; fx = fraction; ECOG = Eastern Cooperative Oncology Group; AUC = area under the curve.

TABLE II Treatment outcomes

Reference	*Arm*	*Survival*				*Objective response rate*	
		Overall		*Progression-free*		*Median*	*Comparison*
		Median (months)	*Comparison*	*Median (months)*	*Comparison*	(%)	
Bonner *et al.,* 2006 [10]	RT	29.3	HR: 0.74 (range: 0.57 to 0.97)	12.4	HR: 0.70 (range: 0.54 to 0.90)	64	OR: 0.57 (CI: 0.36 to 0.90)
	RT+C	49.0	$p = 0.03$	17.1	$p = 0.006$	74	$p = 0.02$
Burtness *et al.,* 2005 [6]	CT+P	8.0 (CI: 6.1 to 10.6)	$p = 0.21$	2.7 (CI: 1.9 to 3.8)	$p = 0.09$	26	$p = 0.03$
	CT+C	9.2 (CI: 7.1 to 12.1)		4.2 (CI: 3.7 to 5.5)		10	
Vermorken *et al.,* 2008 [20]	Cis	7.4 (CI: 6.4 to 8.3)	HR: 0.80 (range: 0.64–0.99)	3.3 (CI: 2.9 to 4.3)	HR: 0.54 (range: 0.43–0.67)	20 (CI: 15 to 25)	OR: 2.33 (CI: 1.50 to 3.60)
	Cis+C	10.1 (CI: 8.6 to 11.2)	$p = 0.04$	5.6 (CI: 5.0 to 6.0)	$p<0.001$	36 (CI: 29 to 42)	$p<0.001$
Stewart *et al.,* 2007 [19] (abstract)	M	6.7	HR: 1.22 (CI: 0.95 to 1.57) $p = 0.12$	NR		3.9	NS
	G250	5.6	HR: 1.12 (CI: 0.87 to 1.43) $p = 0.39$			2.7	
	G500	6.0				7.6	

RT = radiation therapy; C = cetuximab; HR = hazard ratio; OR = odds ratio; CI = 95% confidence interval; CT = chemotherapy; P = placebo; Cis = cisplatin; M = methotrexate; G250 = gefitinib 250 mg once daily; G500 = gefitinib 500 mg once daily; NR = not reported; NS = nonsignificant.

($p < 0.01$), which were significantly higher in the cetuximab group. It was noted that cetuximab did not exacerbate any of the adverse events that commonly occur when patients receive radiation for head-and-neck cancer [10].

Burtness *et al.* [6] reported that 90% of patients in the cisplatin–cetuximab group and 73% in the cisplatin–placebo group experienced grade 3 or 4 adverse effects ($p = 0.02$). Hypomagnesemia (14% vs. 0%, $p = 0.006$) and neutropenia (30% vs. 14%, $p = 0.04$) were more common in the cisplatin–cetuximab arm than in the cisplatin–placebo group. Additionally, overall hematologic toxicity occurred in 36% of patients receiving cisplatin plus cetuximab as compared with 18% of patients receiving cisplatin alone ($p = 0.04$). Skin toxicity was reported in 77% of patients receiving cisplatin plus cetuximab as compared with 23% of patients receiving cisplatin alone ($p < 0.001$). Because development of a rash was such a common adverse event, placebo use was considered an ineffective tool for blinding patients and investigators to treatment assignment [6].

Vermorken *et al.* [20] reported that the incidence of any adverse event was similar between study groups, with 82% of patients in the cetuximab group and 76% in the chemotherapy-alone group reporting an event ($p = 0.19$). No differences were reported between groups for adverse incidences of neutropenia (22% vs. 23%, $p = 0.91$), thrombocytopenia (11% vs. 11%, $p = 1.00$), leucopenia (9% vs. 9%, $p = 1.00$), or anemia (13% vs. 19%, $p = 0.12$). However, the cetuximab group had a greater incidence of skin reactions (9% vs. <1%, $p < 0.001$), anorexia (5% vs. 1%, $p = 0.05$), hypomagnesemia (5% vs. 1%, $p = 0.05$), and sepsis (4% vs. <1%, $p = 0.02$), including septic shock [20].

Stewart *et al.* reported an increased percentage of patients with incurable advanced recurrent HNSCC experiencing tumour hemorrhage with gefitinib (250 mg daily: 8.9%; 500 mg daily: 11.4%) than with weekly methotrexate (1.9%) [19].

4.4 Quality of Life

Data concerning QOL were published separately for the RCT reported by Bonner *et al.* [10] The Quality of Life Questionnaire C30 [22] was used to assess patients initially (at baseline), and at week 4 and months 4, 8, and 12. Of the 419 patients assessable for QOL, only 164 (39%) had completed the questionnaire at all visits. The authors commented that, even though considerable differences were detected between baseline and worst post-baseline multi-item symptom scores across all scales, no statistical difference in overall QOL was observed between the two treatment groups. The most notable differences in mean score for the radiation-alone group compared with the radiation and cetuximab group involved sensory problems (39.5 vs. 41.2, $p = 0.598$) and trouble with social contact (16.6 vs. 20.1, $p = 0.472$). Analysis using pattern-mixture models for the global health status (QOL) and social functioning scales indicated no significant treatment difference between the two treatment arms ($p = 0.103$ and $p = 0.855$ respectively) [21].

Two of the sixteen multi-item scales showed a significant difference between treatment arms, both in favour of radiation–cetuximab at week 4: the swallowing scale (difference in least square means scores: –8.12; $p = 0.004$) and the speech problems scale (difference in least square means scores: –5.92, $p = 0.028$) [21]. Given that the differences were small and the results were not supported at other time points or by summary measure analysis, it is possible that these results occurred by chance because of multiple testing [21].

5. EXTERNAL REVIEW RESULTS

Four responses were received from four reviewers. Table III summarizes key results of the feedback survey. The substantive comments received from external review are presented here together with the responses from the DSG:

- ***Comment:*** "The comment about chemoradiation not being suitable for patients > 70 needs to be tempered somewhat. Some 70-year-old patients are more like 50-year-olds, and I would not necessarily deny them concurrent chemo/XRT."
  Response: The recommendations herein are to be used by the physician as guidance; however, the Head and Neck Cancer DSG recognizes that decision-making regarding treatment should occur on a case-by-case basis.

- ***Comment:*** "The fully published Vermorken paper is now available [Vermorken *et al.* 2008 [20]]. This makes the recommendations about adding cetuximab to chemotherapy in the metastatic setting out of date already. The guideline needs to be updated with this information."
  Response: The results from the fully published Vermorken trial were added to the document, and the qualifying statement based on the Vermorken trial was moved to the Recommendations section now that it is based on fully published data.

- ***Comment:*** "In the discussion about gefitinib in the Introduction, this drug is no longer approved for use by either Health Canada or the FDA in NSCLC [non-small-cell lung cancer]. It should be emphasized that, in December 2006, Health Canada reported a lack of survival benefit and increased incidence of tumour hemorrhage in association with gefitinib in HNSCC. The sentence (page 2) 'additionally, gefitinib can also improve the efficacy of cytotoxic agents, radiation and hormone therapies' is sweeping and needs to be substantiated by evidence."

TABLE III Responses to eight items on the targeted peer reviewer questionnaire

Question	*Lowest quality* 1	2	3	4	5	6	*Highest quality* 7
Rate the guideline development methods:					1	3	
Rate the guideline presentation:				1	1	1	1
Rate the guideline recommendations:			1	1	1	1	
Rate the completeness of reporting:			1	2			
Does this document provide sufficient information to inform your decisions?				1	1	1	
If not, what areas are missing?							
Rate the overall quality of the guideline report:				2	1	1	
	Strongly disagree 1	2	3	4	5	6	*Strongly agree* 7
I would make use of this guideline in my professional decisions:			2	1	1		
I would recommend this guideline for use in practice:			2	1	1		
What are the barriers or enablers to the implementation of this guideline report?	Funding of drugs. Lack of long-term safety (long toxicity) data. The lack of available level 1 data on chemosparing and chemoadditive strategies. The moving target of "standard therapy" because of other regimens (for example, sequential therapy). Cetuximab is not currently available in Canada. Cost of cetuximab. Is it covered by the government? Funding and availability of EGFR-targeted therapy						

EGFR = epidermal growth factor receptor.

Response: As suggested, the information pertaining to gefitinib in the Introduction was removed, because this drug is no longer approved by Health Canada (lack of survival benefit and increased incidence of severe adverse effects).

- ***Comment:*** "The recommendation to avoid concurrent chemotherapy in patients over the age of 70 and to administer cetuximab to this subgroup is not entirely evidence-based (i.e. the Bonner trial did not specifically demonstrate that patients over 70 had a similar hazard ratio for its primary efficacy endpoint as those below 70). Similarly, the Bonner trial did not specifically evaluate patients "who are medically unsuitable for concurrent platinum-based chemotherapy," hence the recommendation to administer cetuximab to this subgroup to provide benefits in OS [overall survival], PFS [progression-free survival] and LRC [locoregional control] is a bit of a leap of faith. The lack of level 1 evidence for these 2 compromised subgroups of patients renders such a strong recommendation inappropriate, perhaps the wording should be altered to 'consider' rather than 'recommend'—ultimately conducting a proper clinical trial to evaluate them would likely be the most appropriate option, if that is ever possible."
  Response: The working group included the recommendation that patients over the age of 70 years be considered for cetuximab treatment to provide another treatment option for these patients. Concurrent chemotherapy is still a treatment option in this group.

- ***Comment:*** "The lack of data on late toxicity related to the combination with EGFR-targeted therapies and radiation therapy needs to be discussed."
  Response: Currently, no data are available on late toxicity with cetuximab use. A sentence to reflect this fact has been added to the Discussion section.

- ***Comment:*** "The mixture of nonmetastatic stage III and IV trials with metastatic stage IV trials and the lumping together of recommendations for these two prognostically varied groups made the presentation of this guideline somewhat confusing and difficult to follow. It probably would have been clearer to have separate discussions of the evidence and recommendations."
  Response: This document includes patients with nonmetastatic stages III and IV disease and patients with metastatic stage IV disease so as to address the topic with one rather than two documents.

- ***Comment:*** "While the guideline rightfully has focused on phase III randomized trials, it may have been informative to discuss briefly some background summary information about the different types of EGFR inhibitors in clinical development, their safety and toxicity profiles, and the results of relevant phase II trials (e.g. small-molecule EGFR tyrosine kinase inhibitors in recurrent or metastatic HNSCC have single-agent response rates of 0 (lapatinib) to 10.6% (gefitinib))."
  Response: It was decided *a priori* that the document would include only randomized phase II and III trials, as specified in the literature search inclusion criteria, because this evidence is the highest level available.

- ***Comment:*** "The sentence (page 11–12) 'for patients who are candidates for standard chemoradiotherapy, an additional randomized trial confirming the benefits of adding an anti-EGFR monoclonal antibody to RT, or optimally chemoradiotherapy, would be of value.' The words 'additional' and 'optimally' in this sentence needs to be qualified—what do the authors mean by these?"
  Response: "Additional" was removed and "(given that it is the current standard of care)" was added to describe why a randomized trial comparing "optimally, chemoradiotherapy" to anti-EGFR therapy has been suggested.

- ***Comment:*** "The guideline only mentioned that cetuximab has been approved by the FDA for use in combination with radiation in the treatment of patients with previously untreated locally advanced (not just advanced) HNSCC; it did not mention that cetuximab has also been approved as monotherapy for recurrent or metastatic HNSCC patients who have progressed on platinum-based therapy."
  Response: Appropriate changes have been added so that all of the approvals for cetuximab in HNSCC are included.

- ***Comment:*** "The following trial should be mentioned: [Vermorken JB, Trigo J, Hitt R, *et al*. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol* 2007;25:2171–7.]"
  Response: Because the inclusion criteria for the present document specified the use of only randomized phase II/III trials, the mentioned trial is not included.

- ***Comment:*** "Until the clinical trials of anti-EGFR therapy + RT vs. chemoRT (chemosparing) and those of anti-EGFR therapy + chemoRT vs. chemoRT (chemoadditive) are completed, the role of these agents in the locally advanced HNSCC setting is actually unclear to me. The guideline can clarify the evidence, but I do not think it can actually

recommend its use based on existent evidence to those unsuitable to receive concurrent chemoRT. The take-home message should be 'We should strive to obtain better safety and efficacy data on such patient populations in light of lack of evidence,' and not 'Give it since we don't know better what to do with these patients'!"

Response: In paragraph 3 in the Discussion section, ongoing trials investigating chemosparing and chemoadditive regimes are discussed. Additionally, it is stated in paragraph 3, and in the Conclusion section that the results of the ongoing studies are needed to make recommendations in patients under the age of 70 years.

Two responses were received from the professional consultation. Both responders rated as high the overall quality of the guideline, strongly agreed that they would make use of the guideline in their professional decisions, and indicated that they would strongly recommend this guideline for use in practice (all ratings 6 out of 7). Contained within the written comments section were concerns about the lack of funding and expense of EGFR therapies in Ontario.

6. DISCUSSION

For most patients with advanced HNSCC, long-term survival remains poor. The 5-year survival rate, worldwide, from oral cancer is generally less than 50%. Standard treatment for locoregionally advanced HNSCC is radiotherapy with concurrent platinum chemotherapy [3]; treatment for recurrent or metastatic HNSCC is platinum-based chemotherapy [6]. Recently, two RCTs studying cetuximab, a monoclonal antibody to EGFR, have reported improved outcomes for patients with advanced HNSCC. One of these represents the first adequately powered RCT ever to show an overall survival benefit in patients with incurable advanced recurrent or metastatic HNSCC.

6.1 Locally Advanced HNSCC

Bonner *et al.* reported improved locoregional disease control, progression-free survival, and overall survival with the addition of cetuximab to radiation in patients with locally advanced HNSCC [10]. Chemoradiation is currently considered optimal therapy for this group of patients [3]. However, concurrent chemotherapy is not only associated with additional adverse effects such as nausea, vomiting, and neutropenia, but also with severe oropharyngeal mucositis in more than 50% of patients. This latter adverse event represents a serious challenge to QOL, costs, and management in these patients. A large meta-analysis of individual patient data has also reported that concurrent chemotherapy is not associated with an improvement in overall survival in patients over the age of 70 years [4]. It is unclear whether this lack of efficacy is a result of one or some combination of reduced efficacy of treatment, increased mortality of treatment, and effects of competing risks. The addition of cetuximab to radiation was not associated with chemotherapy-specific toxicities or an increase in the frequency of severe mucositis beyond that seen with radiation alone [10]. The most common and significant effect was skin rash, which occurred in 87% of patients. The rash was severe in 17% of patients. Acute infusion reactions also occurred in 3% of patients. Overall QOL was neither improved nor diminished by the addition of cetuximab to radiation.

Although subgroup analyses of randomized trials should be interpreted with caution, they may be of value in assessing the validity and generalizability of the results of a single RCT to clinical practice. Data reported by Bonner *et al.* indicate a disproportionate benefit of the addition of cetuximab to RT in patients with oropharyngeal cancer and in patients treated with hyperfractionated radiotherapy. These results could be attributable to chance alone; however, with recent recognition of the improved prognosis of human papilloma virus (HPV)–related oropharyngeal cancer, it is conceivable that a chance imbalance in HPV-related oropharyngeal cancer could explain much of the benefit derived from the addition of cetuximab [23]. Thus, for patients in whom standard chemoradiotherapy is neither an option nor effective, cetuximab is considered reasonable based on the results of Bonner *et al.* Data pertaining to late toxicity of cetuximab in patients with HNSCC are lacking. Future trials should investigate the long-term safety of cetuximab and other EGFR inhibitors. For patients who are candidates for standard chemoradiotherapy, a randomized trial confirming the benefits of adding an anti-EGFR monoclonal antibody to RT—or optimally, chemoradiotherapy (given that it is the current standard of care)—would be of value.

6.2 Recurrent or Metastatic HNSCC

Patients with incurable advanced recurrent or metastatic HNSCC studied in RCTs have a median survival of 6 months. Combination platinum-based chemotherapy is the standard of care and achieves higher response rates than does active single-agent therapy, but in RCTs, combination therapy is associated with greater toxicity and no clear increment in overall survival [24].

A recent RCT compared the commonly used combination of cisplatin–5-fluorouracil with paclitaxel–cisplatin; no clinically important differences in response rate, QOL, or overall survival were observed [24]. Two RCTs have studied the addition of cetuximab to platinum–5-fluorouracil chemotherapy in first-line treatment in these patients [6,20], and one of those two trials reported improved overall survival, progression-free survival, and overall tumour response rate [20]. Those results represent the first indication, demonstrated in a large, adequately powered RCT, of improved overall survival with any treatment in this group of patients.

Far fewer data are available from clinical trials involving patients with incurable advanced recurrent or metastatic HNSCC who have suffered disease progression despite prior chemotherapy or who are unsuitable for platinum-based chemotherapy. Stewart *et al.* compared two different doses of daily gefitinib, a small-molecule EGFR tyrosine kinase inhibitor, with weekly intravenous methotrexate in this group of patients and identified no overall survival benefit [19]. The rate of tumour hemorrhage was increased in both gefitinib arms and may have contributed to unproven, but unfavourable, HRS associated with gefitinib. Health Canada recently issued a statement based on the findings of the Stewart *et al.* study, informing patients using gefitinib that, in most cases, tumour hemorrhage was mild to moderate and did improve, but that 3 patients had died as a result of the bleeding [25].

Recently, information about the utility of using KRAS, a downstream G protein in the EGFR signalling cascade, as a biomarker to determine which patients with colon cancer will benefit from the addition of EGFR inhibitors to best supportive care treatment has emerged. Two RCTS found that patients expressing the wild-type *KRAS* genotype treated with best supportive care plus an EGFR inhibitor (cetuximab or panitumumab) experienced increased progression-free survival [26,a], overall survival [a], and tumour response rate [26]. However, patients who expressed the mutant *KRAS* genotype did not benefit from the addition of an EGFR inhibitor to best supportive care [26,27]. To date, no study has investigated whether *KRAS* genotype influences the effectiveness of EGFR inhibitors with regard to any meaningful outcomes in HNSCC. However, it has been established previously that *KRAS* mutations are uncommon in HNSCC [28], and thus testing for *KRAS* mutations before treatment with EGFR inhibitors is not recommended in HNSCC.

7. PRACTICE GUIDELINE

This clinical practice guideline is based on work completed in May 2009. Practice guidelines developed by the PEBC are reviewed and updated regularly. Please visit the Cancer Care Ontario Web site (www.cancercare.on.ca) for a complete list of current projects and subsequent updates.

7.1 Recommendations

These recommendations are based on evidence derived from a systematic review of the literature, interpretation by the Head and Neck Cancer DSG, and input from internal and external review participants in Ontario:

Platinum-based chemoradiation remains the current standard of care for treatment of locally advanced HNSCC.

In patients with locally advanced HNSCC who are medically unsuitable for concurrent platinum-based chemotherapy or who are over the age of 70 years (because concurrent chemotherapy does not appear to improve overall survival in this patient population), the addition of cetuximab to radical radiotherapy should be considered to improve overall survival, progression-free survival, and time to local recurrence.

Cetuximab in combination with platinum-based combination chemotherapy is superior to chemotherapy alone in patients with recurrent or metastatic HNSCC, and is recommended to improve overall survival, progression-free survival, and response rate.

The role of anti-EGFR therapies in the treatment of locally advanced HNSCC is currently under study in large randomized trials, and patients with HNSCC should continue to be offered clinical trials of novel agents aimed at improving outcomes.

7.2 Qualifying Statements

Chemoradiation is the current standard of care for patients with locally advanced HNSCC, and to date, there is no evidence that compares cetuximab plus radiotherapy with chemoradiation or that examines whether the addition of cetuximab to chemoradiation is of benefit to these patients. However, five ongoing trials are investigating the effect of the addition of EGFR inhibitors concurrently with, before, or after chemoradiotherapy; they should provide direction about the best integration of cetuximab into standard treatment.

In patients with recurrent or metastatic HNSCC who experience progressive disease despite, or who are unsuitable for, first-line platinum-based chemotherapy, gefitinib at a dose of 250 mg or 500 mg daily, compared with weekly methotrexate, did not increase median overall survival [HR: 1.22; 96% CI: 0.95 to 1.57; $p = 0.12$ (for 250 mg daily vs. weekly methotrexate); HR: 1.12; 95% CI: 0.87 to 1.43; $p = 0.39$ (for 500 mg daily vs. weekly methotrexate)] or objective response rate (2.7% for 250 mg daily and 7.6% for 500 mg daily vs. 3.9% for weekly methotrexate, $p > 0.05$) [5]. Daily gefitinib, as compared with weekly methotrexate, was associated with an increased incidence of tumour hemorrhage (8.9% for 250 mg daily and 11.4% for 500 mg daily vs. 1.9% for weekly methotrexate).

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